PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 040826woMemh	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/003115	International filing date *(day/month/year)* 24.03.2004	Priority date *(day/month/year)* 24.03.2003
International Patent Classification (IPC) or national classification and IPC A61K38/19		
Applicant IPF PHARMACEUTICALS GMBH et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.01.2005	15.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Didelon, F Telephone No. +49 89 2399-7332

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003115

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-12 as originally filed

   Claims, Numbers

   1-9 filed with telefax on 24.01.2005

   Drawings, Sheets

   1/1 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6-9 (IA)

because:

☒ the said international application, or the said claims Nos. 6-9 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 6-9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Said claim seem to depend on use claims but are formulated as method claims. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1 : MOLLER C ET AL: "Expression and function of chemokine receptors in human multiple myeloma." LEUKEMIA (BASINGSTOKE), vol. 17, no. 1, 20 January 2003 (2003-01-20), pages 203-210, XP002252455 ISSN: 0887-6924

D2: WRIGHT DOUGLAS E ET AL: "Hematopoietic stem cells are uniquely selective in their migratory response to chemokines." JOURNAL OF EXPERIMENTAL MEDICINE, vol. 195, no. 9, 6 May 2002 (2002-05-06), pages 1145-1154, XP002252456 May 6, 2002 ISSN: 0022-1007

D3: WO 00/46248 A (SCHERING CORP) 10 August 2000 (2000-08-10)

D4: WO 01/17558 A (SCHERING CORP) 15 March 2001 (2001-03-15)

D5: US 2003/049696 A1 (GEORGE THADDEUS C ET AL) 13 March 2003 (2003-03-13)

D6: WO 00/73432 A (CORNELL RES FOUNDATION INC) 7 December 2000 (2000-12-07)

D7: WO 00/03016 A (CONNEX GMBH ;REITER CHRISTIAN (DE)) 20 January 2000 (2000-01-20)

D8: CA 2 256 250 A (UAB FOUNDATION, US) 17 June 1999 (1999-06-17)

Unless otherwise indicated, the relevant passages in the cited documents are the ones

indicated in the Search Report.

2. Novelty and inventive step :

D1 reveals that multiple myelomas cells migrate in response to chemokines SDF-1, MIP-1alpha and RANTES. This could be used as a new treatment for multiple myeloma. However it does not disclose stem cells.

D2 reports that, contrary to the present application, hematopoietic stem cells only respond to SDF-1, ligand of CXCR-4 receptor but not to other chemokines. However the combination of both SDF-1 and other chemokines is effective. The specific chemokine ligands of CCR-3 -6 an d-8 are however not effective on the migration of hematopoietic stem cells.

In D3 and D4, MIP-3alpha or CCR6 agonist are contemplated for use in some diseases, including skin grafts. However stem cells are not encompassed in the disclosure and the goal is not of enhancing homing of stem cells but to reduce inflammatory response against said grafts.

D5 discloses the trafficking of regulatory T-cells is modulated by agonists of CCR6, e.g., MIP-3alpha or LARC. This finds usefulness in transplantation and in modulation of immune response. This document however does not deal with the migration of stem cells.

D6 describes SDF-1 and MIP-3alpha, delivered through adenoviral vectors, and able to attract dendritic cells in vitro and are thus used to enhance immunity, in particular to combat cancers.
Again stem cells are not encompassed in said document.

D7 reveals that RANTES, MIP-1alpha (CCR3 agonists), MIP-1beta (CCR8 agonist) are used as pharmaceutical compositions for prevention of autoimmune diseases, immune deficiencies, infectious diseases, suppression of immune response in graft rejection. It does not relate however to the improvement of stem cell migration for increasing transplantation efficiency.

D8 disclosed chemokines such as RANTES, MIP-1alpha, MIP-1beta used as mucosal immune enhancers.

It is understood that a novel cellular mechanism has been discovered, in that the ligands of different chemokines receptors have been found to potentiate the effects of the CXCR4 receptor ligand SDF-1 for improving stem cell transplantation.
Claim 1 which satisfactorily defines the medical application underlying the present application "treatment of progenitor/stem cells prior to and/or in the course of transplantation" is thus considered as novel and inventive because the prior art does not reveal nor suggest the treatment of progenitor or stem cells used in the application for improving transplantation.

3. For the assessment of the present claims 6-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. For the sake of completeness, it must be made clear that in front of some regional Authorities, human embryonic stem cells (see claim 3) are not to be encompassed within the scope of the present application.

Claims

1. The use of at least one agonist of receptors selected from the group consisting of the CCR3, CCR6 or CCR8 receptor or combinations thereof and a pharmaceutically acceptable carrier for treatment of progenitor and stem cells prior to and/or in the course of transplantation of the cells wherein the agonist is selected from the group consisting

   of receptor CCR3: Eotaxin; Eotaxin-2; Eotaxin-3 ; Hemofiltrate CC-Chemokine-1 (HCC-1); Hemofiltrate CC Chemokine-2 (HCC-2); Macrophage Inflammatory Protein – 1α (MIP-1α); Regulated on Activation Normally T-Cell Express and Secreted (RANTES); Monocyte Chemoattractant Protein – 2 (MCP-2); Monocyte Chemoattractant Protein – 3 (MCP-3); Monocyte Chemoattractant Protein – 4 (MCP-4); 2-[(6-amino-2-benzothiazolyl)thio]-N-[1-[(3,4-dichlorylphenyl)methyl]-4-piperidinyl] acetamide;

   of receptor CCR6: Macrophage Inflammatory Protein – 3α (MIP-3α);

   of receptor CCR8: I309; Macrophage Inflammatory Protein – 1β (MIP-1β); LAG-1; Thymus and Activation Regulated Chemokine (TARC); viral Macrophage Inflammatory Protein – I (vMIP-I); as well as derivatives therof keeping their agonist abilities.

2. The use of claim 1 for improving the homing of stem cells.

3. The use according to one or more of the foregoing claims for the transplantation of hematopoietic progenitor and stem cells, umbilical cord blood and placental stem and progenitor cells, liver stem and progenitor cells (oval cells), mesenchymal stem and progenitor cells, endothelial progenitor cells, skeletal muscle stem and progenitor cells (satellite cells), smooth muscle stem and progenitor cells, intestinal stem and progenitor cells, embryonic stem cells, and genetically modified embryonic stem cells, adult islet/beta stem- and progenitor cell, epidermal progenitor and stem cells, keratinocyte stem cells of

cornea, skin and hair follicles, olfactory (bulb) stem and progenitor cells and side population cells from diverse adult tissues.

4. The use according one or more of the foregoing claims to increase the sensitivity of hematopoietic stem cells to SDF-1 induced cellular signals.

5. The use according one or more of the foregoing claims for the treatment of leukemias, lymphoproliferative disorders, aplastic anemia, congenital disorders of the bone marrow, solid tumors, autoimmune disorders, inflammatory diseases, primary immunodeficiencies, primary systemic amyloidosis, systemic sclerosis, heart diseases, liver diseases, neurodegenerative diseases, multiple sclerosis, M. Parkinson, stroke, spinal cord injury diabetes mellitus, bone diseases, skin diseases, replacement therapy of the skin, retina or cornea, other congenital disorders, vessel diseases like atherosclerosis or cardiovascular disease.

6. The method of the foregoing claim wherein the host patient are not conditioned.

7. The method of claim 6 wherein the host patient is conditioned under sublethal, lethal, or supralethal conditions.

8. The method according to claim 7 wherein sublethal, lethal, or supralethal conditions include treatment with total body irradiation, optionally followed by treatment with myeloablative or immunosuppressive agents.

9. The method according to any one of the claims 7 or 8 wherein sublethal, lethal, or supralethal conditions include myeloablative or immunosuppressive treatment without total body irradiation.